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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WYETH
PATENT LAW GROUP
5 GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,619	O'TOOLE ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,8 and 22* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5, 8, 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 10/23/2007. Currently Claims 1-2, 4-5, 8, and 22 are pending. Claims 3, 6-7, 9-21 have been cancelled. Claim 4 has been withdrawn as being drawn to a nonelected invention.

2. This application contains claim 4 drawn to an invention nonelected with traverse in the reply filed on 1/11/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. The following rejections to Claims 1-2, 5, 8, and 22 are reiterated. Response to arguments follows.

4. This action is FINAL.

Reiterated Rejections

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 5, 8, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of identifying an increased likelihood of lupus nephritis in a mouse, the method comprising the steps of:

a) Obtaining a kidney sample from a control mouse and a mouse of interest

b) Detecting an expression level of the midkine mRNA transcript in the kidney sample of the control mouse and the mouse of interest

c) Comparing the midkine mRNA transcript level of the control mouse and the mouse of interest, wherein an increased expression level of the midkine mRNA transcript level of the mouse of interest relative to the expression level of the midkine mRNA transcript level indicates that the mouse of interest has an increased likelihood of lupus nephritis.

does not reasonably provide enablement for methods to diagnose lupus nephritis (LN) in human by detecting an elevated expression level of midkine gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims

The claims are broadly drawn to diagnosing lupus nephritis in a human or a mouse comprising detecting the expression level of midkine gene in a kidney sample wherein an elevated expression level indicates an increased likelihood of lupus nephritis. The claims are broadly drawn to both human and mouse.

The invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification

The specification teaches systematic lupus erythematosus (SLE) is an autoimmune disease that has diverse and variable clinical manifestations that range from skin rash and joint pain that can show spontaneous remissions to severe kidney disease that may result in renal failure, otherwise known as lupus nephritis (LN). Midkine (MDK) has several functions including neural-glial interactions in brain development, inflammation, tumor and angiogenesis, and anti-apoptotic activities (specification, pages 14-19). The specification asserts that midkine is a marker for SLE or LN, and its expression can be utilized as a diagnostic for said diseases (page 4). The specification concludes "MDK has not previously been associated with SLE and LN.....While mouse models were used for the initial differentiation expression analysis; it is well-appreciated that animal models can be interpreted to reflect

expression levels from human subjects as well. The present invention...encompasses human MDK" (page 22). The specification further asserts "without limitation as to mechanism, the present invention is based in part on the principle that modulation of the expression of the MDK gene expression may ameliorate SLE/LN, when they are expressed at levels similar or substantially similar to normal non-diseased tissues" (page 23).

The specification discloses working examples of the isolation of RNA from kidney samples of several different mouse models of lupus that ranged in age of five months to 8, 16, 20 weeks of age, thus representing early, intermediate, and late stages of lupus, and control mice of the same age range. The working examples disclose that after the isolation of kidney tissues from said mice, RNA was isolated and cDNA was synthesized, and then the samples were analyzed with Affymetrix Mu11KsubA and Mu11KsubB microarrays. Statistical analysis was subsequently performed, and TaqMan assays were performed on genes of interest (pages 13-14 and 78-82).

State of the Prior Art

Kotzin et al. teaches (Cell, 1996, Vol. 85, pages 303-306) the underlying cause of lupus has yet to be determined as environmental factors such as sun exposure, viral or bacterial infections, hormonal and drug treatments, and genetic contributions play a role in the manifestation of the disease (Kotzin, page 305). Kotzin teaches several animal models have been used to study lupus, however, due to the complex nature of the disease, "even when one animal model and one

phenotype is considered, the genetic basis of lupus-like disease is remarkably complex, involving contributions from multiple genes in addition to class II MHC....Furthermore, it seems likely that different genetic contributions are operative in different animal models (and therefore in different patients), even when the same phenotype is being followed" (page 305). Kotzin further teaches mouse models are used to study the genetic causes of lupus, and to predict human genes that are associated with said disease since mouse and human genes are homologous (Journal of Clinical Investigation, 1997, Vol.99, No. 4, pages 557-558). However, as stated above, environmental factors and phenotypic expression of lupus have considerable variation, and since the environment conditions are controlled for animal studies and the animal models are bred to have uniform lupus symptoms, it is unclear if results from animal studies can be applicable to humans. Kotzin teaches, "disease phenotype among mice in each cross is much more uniform compared to the relatively heterogeneous disease expression in patients. Especially in SLE, clinical manifestations and autoantibody production can be extremely diverse and variable, which is in part genetically based, and this variability can confound genetic studies" (Journal of Clinical Investigation, page 557). To ensure accurate predictions of the results of mouse lupus models to humans "there should also be concern that an initial mapping in a complex trait reflects false positive readings....If true, this human locus...may not be in a region synthenic to the murine susceptibility locus, and linkage in the current human study would therefore represent quite a fortuitous finding," and in order to ensure accurate

results, large studies of human patients will need to be performed (Kotzin, Journal of Clinical Investigation, page 558).

The Relative Skill of Those in the Art

The level of skill in the art is deemed to be high.

The Predictability or Unpredictability of the Art and Degree of Experimentation

Moreover, as indicated by Kotzin et al., an animal model may not be an accurate representation of another animal's response to lupus. Genetic homology does not necessarily correlate to phenotypic expression. As mentioned previously, environmental factors play a role in the development of lupus, and it is unpredictable if a mouse, particularly in a controlled environment, will react in the same manner to environmental factors as humans.

Liu et al. (Clinical Immunology 2004 Vol. 112 p. 225) teaches that that correlation of genes to disease traits in mouse models is not indicative of correlation in humans. Liu et al. teaches that the gene expression profile of humans with autoimmune disease is not the same as the gene expression in a mouse model and in fact there is very little overlap in the gene expression profile of the two (Abstract). Liu et al. found that there was no overlap between the differentially expressed genes between human and mouse data sets with regard to systemic lupus (p. 228 1st column 1st paragraph). Liu et al. teaches that their results show that murine models do not perfectly model corresponding human

autoimmune diseases when gene expression profiles are considered (p. 229 2nd column last paragraph).

Morel et al. (PLOS Biology August 2004 Vol. 2 p. 1061) teaches that one cannot directly apply data obtained from animal models to human diseases (p. 1062 1st column last paragraph). Morel et al. teaches that human autoimmune diseases (which includes lupus) show extremely heterogeneous clinical presentation and that animal models only present a simplified version (p. 1062 1st column last paragraph). Morel et al. teaches the mouse model only provides a partial representation of the real biological complexity underlying the human disease (p. 1062 1st column last paragraph). Morel et al. teaches that extrapolation from animal models to autoimmune patients are limited by the differences between the two immune systems (p. 1062 2nd column 1st paragraph).

Consequently, it is unpredictable if a mouse phenotypic expression of lupus will be similar to humans. Consequently, the skilled artisan would have to examine midkine's expression in As a result, the specification does not teach the person skilled in the art how to reasonably predict, without undue burden, SLE or LN by midkine expression levels in a biological sample of human.

Amount of Direction or Guidance Provided by the Specification

Though the specification provides working examples of mouse models with regard to the detection and correlation of elevated expression levels of midkine gene, the specification has not provided sufficient guidance to extrapolate these results to human. Further the

art teaches that correlations in mouse models are not sufficient to correlate expression in humans. The art also teaches that expression profiles of genes differ in humans afflicted with autoimmune disease and mouse models with autoimmune disease. Therefore the specification has not provides sufficient guidance to one skilled in the art to correlate elevated midkine levels to lupus in humans. Further the skilled artisan would have to perform undue experimentation to correlate midkine levels with lupus in humans because the art teaches that correlations in mouse models cannot be extrapolated to humans without intervening experimental steps, which have no guarantee of success.

Working Example

The specification does not provide working examples of methods to diagnose lupus with midkine expression levels in human. The methods do not demonstrate the methodology can be used to predictably diagnose lupus with midkine mRNA in humans.

Conclusions

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable

correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genentech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In view of the high level of unpredictability in the art and lack of guidance provided by the specification and prior art, undue experimentation would be required to practice the claimed invention.

1.132 Declaration and Response to Arguments

The 1.132 declaration under 37 CFR 1.132 filed 10/23/2007 is insufficient to overcome the rejection of claims 1-2, 5,8, and 22 based upon 35 USC/112 Enablement as set forth in the last Office action. The response to arguments traverses the 35 USC/112 Enablement.

The 1.132 declaration and the reply traverse the rejection. The arguments made in the 1.132 declaration and the reply are summarized and discussed below.

(A) Margot M. O'Toole declares in the declaration under 37 CFR 1.132 that the parent application determined that the midkine gene expression was elevated in kidney samples of lupus nephritis-affected mice when compared to controls (p. 2 point 2). The 1.132 asserts the strains of lupus nephritis affected mice are extensively used in the art to study lupus and the signs and symptoms

exhibited by these mice closely parallel those observed in humans including auto-antibody production and glomerular nephritis (p. 2 point 2).

This argument has been fully considered but has not been found persuasive.

Though, their might be genetic or phenotypic parallels between mouse models and humans for certain gene expressions it is not predictable that all genes expressed in a mouse model will be correlative to expression levels in a human. In the instant case, the specification teaches a correlation of increased midkine gene expression in a mouse model with lupus. However, based on the teaching in the art, Kotzin et al. (1 and 2), Morel et al., and Liu et al. a direct correlation between expression in a mouse model and expression in a human is unpredictable. Therefore although a mouse model has a correlation between increased expression of the midkine gene and lupus such a correlation cannot be predictably extrapolated to humans.

(B) The 1.132 asserts that nothing in the Kotzin 1 reference suggests a lack of correlation between elevated midkine gene expression and increase likelihood of lupus in humans (p. 2 point 4). The 1.132 asserts that there are observations in Kotzin 1 which support the extrapolation of mice to human disease (p. 2 point 4). The 1.132 asserts that Kotzin 1 teaches that animal models have contributed greatly to the elucidation of systemic lupus erthematosus pathogenesis in humans (p. 3 point 4). The 1.132 asserts that Kotzin 1 teaches identification of autoantibodies and their presence in lupus in

patients and mice and therefore Kotzin supports the extrapolation of genetic characteristics in lupus in mice to humans with lupus (p. 3 point 4). The reply further asserts that the change in midkine expression does not mean that a human will necessarily develop lupus or leading to phenotypic expression of lupus but that elevated midkine gene expression is associated with an increased likelihood of lupus (p. 5 3rd paragraph). The reply asserts that nothing in Kotzin 1 suggests a lack of correlation between elevated midkine gene expression and increased likelihood of lupus (p. 5 last paragraph). The reply asserts that Kotzin 1 teaches identification of autoantibodies and their presence in lupus in patients and mice and thus supports extrapolation of genetic characteristics in lupus mice to humans with lupus (p. 5 last paragraph and p. 6 1st paragraph).

This argument has been fully considered but has not been found persuasive.

Though Kotzin et al. (Cell 1996 Vol 85 p. 303) teaches that mouse models have contributed greatly to the elucidation of lupus in humans, it still shows the unpredictability of extrapolating the correlation of genes of lupus mice to humans. Further, the issue here is not the suitability of the mouse models, rather whether the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be predictability used to determine likelihood of detecting higher incidence of lupus.

For example, Kotzin et al. detected an association of defects in lpr and gld in mice models to lupus (p. 305 last paragraph). Kotzin et al. teaches that there is no counterpart to the lpr or gld phenotype in human SLE and in recent studies

there have been no defects found of these genes in SLE patients (p. 306 1st paragraph).

Therefore though mouse models are used to detect potential correlations between genes and disease, there is still a large degree of unpredictability in extrapolation to humans. Therefore, in the instant case, the specification provides a correlation of mouse midkine gene to increase susceptibility to lupus. Neither the specification nor the art of record have provided any guidance that the midkine genes of mouse and humans are expressed similarly. Neither the art nor the art of record teach whether the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be predictability used to determine likelihood of detecting higher incidence of lupus. The skilled artisan would have to perform numerous experiments to determine if there is an association of increased expression of the midkine gene to lupus in humans. As shown in Kotzin et al. this would be unpredictable because genetic associations in mouse models (e.g. lpr and gld) are not always correlative to associations in humans (e.g. in the case of Kotzin et al. no defects of these genes are found in SLE patients).

(C) The 1.132 asserts that Kotzin 2 teaches that NZB X NZW mice are one of the best studied models of lupus nephritis (p. 3 point 5). The 1.132 asserts that Figure 4 of the instant application show that NXB X NZW mice have elevated levels of midkine gene expression correlating with lupus and that these are closely parallel to those observed in humans with lupus (p. 3 point 5). The

reply further asserts that Kotzin 2 teaches NXB X NXW is one of the best-studied models of lupus nephritis and therefore Kotzin 2 supports extrapolation of genetic characteristics of lupus in mice to humans with lupus (p. 6 2nd paragraph).

This argument has been fully considered but has not been found persuasive.

Kotzin et al. (J. Clin Invest 1997 VOl. 99 p 557) teaches to ensure accurate predictions of the results of mouse lupus models to humans "there should also be concern that an initial mapping in a complex trait reflects false positive readings....If true, this human locus...may not be in a region synthenic to the murine susceptibility locus, and linkage in the current human study would therefore represent quite a fortuitous finding," and in order to ensure accurate results, large studies of human patients will need to be performed(p. 558 1st column last fully paragraph). Kotzin et al. teaches that initial mapping of a complex trait in a mouse can lead to false positive findings (p. 558 1st column last fully paragraph).

Therefore though, Kotzin et al. teaches that the mouse model is a good model for human SLE disease there still a high degree of unpredictability to extrapolate an association of a gene and disease from a mouse model to a human model. The issue here is not the suitability of the mouse models, rather whether the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be predictability used to determine likelihood of detecting higher incidence of lupus.

In the instant case, the specification provides a correlation between an increase in gene expression and a higher incidence of lupus in a mouse model. However, there is a high degree of unpredictability in correlating the same elevated expression in a human, because the art teaches that correlations in mouse models are sometimes false positives. Therefore the skilled artisan would have to perform undue experimentation to determine in any human population if there is an elevated expression of the midkine gene associated with higher incidence of lupus. This would require many intervening steps with no expectation of success.

(D) The 1.132 asserts that Liu et al. teaches expression data that is limited to NOD and NZM mouse strains and that neither of these two mouse strains is a good model of lupus nephritis and therefore these observations do not refute the results observed in the instant application can be extrapolated to humans (p. 3 point 6). The reply asserts, that the instant specification shows a positive correlation of midkine gene expression with lupus in mouse models (p. 6 last paragraph). The reply asserts that Liu's observations in NOD and NXM mice does not refute that the results in the instant application can be extrapolated to humans (p. 7 1st paragraph).

This argument has been fully considered but has not been found persuasive.

Though the observations of Liu et al. are not using the same mouse models, it does disclose the expression differences between mouse models and

humans in four distinct autoimmune diseases (p. 227 2nd paragraph 1st full paragraph). Further, the issue here is not the suitability of the mouse models, rather whether the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be predictability used to determine likelihood of detecting higher incidence of lupus.

Liu et al. teaches that the gene expression profile of humans with autoimmune disease is not the same as the gene expression in a mouse model and in fact there is very little overlap in the gene expression profile of the two (Abstract). Liu et al. found that there was no overlap between the differentially expressed genes between human and mouse data sets with regard to systemic lupus (p. 228 1st column 1st paragraph). Liu et al. teaches that their results show that murine models do not perfectly model corresponding human autoimmune diseases when gene expression profiles are considered (p. 229 2nd column last paragraph).

Therefore, the art shows the unpredictability of extrapolating gene expression studies between mouse models and humans. Liu et al. teaches that gene expression of a human and gene expression in mouse data sets do not overlap (p. 228 1st paragraph). In the instant case, the specification and the art do not disclose that the expression level of midkine gene is equivalent in both human and mouse. Neither the specification nor the art of record show a predictability that the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be predictability used to determine likelihood of detecting higher incidence of lupus.

Based on the teachings of other mouse models in Liu et al. and the unpredictability of correlation of gene expression, there is a high degree of unpredictability in extrapolating the findings in the instant specification in a mouse model to humans. The 1.132 and the reply seem to be asserting that the mouse model used in the instant specification is a better model than the ones used in Liu et al. However, there is no evidence that the model used in the instant specification have gene expression equivalent to human populations. The skilled artisan would have to perform undue experimentation to determine in any human population if there is an elevated expression of the midkine gene associated with higher incidence of lupus. This would require many intervening steps with no expectation of success.

(E) The 1.132 and the reply asserts that Furukawa and Yoshimasu refers to the development of MRL/lpr mice which have a mutation in the Fas gene and that based on the observations of Furukawa there is support for the extrapolation of genetic characteristics in lupus mice to humans with lupus (p. 3-4 point 7 and the reply p. 7 2nd paragraph). The 1.132 asserts that the instant application shows that one pathway results in lupus-like symptoms involving elevation of the midkine gene express in the kidney in NZB X NZW in mice, based on the references (Kotzin 2 and Furukawa) there is support for extrapolation from a mouse to human (p. 4 point 8).

This argument has been fully considered but has not been found persuasive.

Furukawa et al. teaches that MRL/lpr mouse is a good model for the spontaneous development of skin lesion similar to those seen in human LE (p 347 1st column 2nd paragraph). Furukawa et al. discloses that it is possible to elucidate the role of the lpr mutation in the development of LE-like skin lesions (p. 347 2nd column 3rd paragraph). Furukawa et al. teaches that skin lesions may be due to the lpr mutation plus additional factors such as environmental stimuli (p. 347 2nd column 3rd paragraph). Furukawa et al. teaches that animal models will become promising tools to investigate the genetic basis in cutaneous lupus (p. 349 last paragraph).

Though Furukawa et al. teaches the use of animals models to detect genetic changes which could be indicative of lupus in human, it does not teach the direct extrapolation of gene expression in a mouse model to human. Further, the issue here is not the suitability of the mouse models, rather whether the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be predictability used to determine likelihood of detecting higher incidence of lupus.

Furukawa et al., rather, teaches that animal models can be a tool to investigate genetic basis but other factors (such as environmental stimuli) must be determined in the human population. Furukawa et al. does not teach that gene expression associations in a mouse model are equivalent in a human population. Therefore, Furukawa et al. does not support a direct extrapolation of mouse model data to human, but rather the use of a mouse model as a tool for further investigation.

(F) The reply asserts that Morel et al. does not contradict or dispute the disclosure to extrapolate genetic characteristic lupus mice to human with lupus (p. 6 2nd full paragraph). The reply asserts that Morel only shows that animal models are a simplified version of human autoimmune disease which are heterogeneous (p. 6 2nd full paragraph).

This argument has been fully considered but has not been found persuasive.

Though Morel et al. does not specifically test the instant gene expression level of midkine in mouse and human with regard to lupus, it does provide details of the unpredictability of such associations. Morel et al. (PLOS Biology August 2004 Vol. 2 p. 1061) teaches that one cannot directly apply data obtained from animal models to human diseases (p. 1062 1st column last paragraph). Further, the issue here is not the suitability of the mouse models, rather whether the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be predictability used to determine likelihood of detecting higher incidence of lupus.

Morel et al. teaches that human autoimmune diseases (which includes lupus) show extremely heterogeneous clinical presentation and that animal models only present a simplified version (p. 1062 1st column last paragraph). Morel et al. teaches the mouse model only provides a partial representation of the real biological complexity underlying the human disease (p. 1062 1st column last paragraph). Morel et al. teaches that extrapolation from animal models to

autoimmune patients are limited by the differences between the two immune systems (p. 1062 2nd column 1st paragraph).

Consequently Morel et al. teaches that findings in mouse models can not be directly correlated in human, but, instead these correlations in mouse models must be tested in human patients and that it is not predictable which genetic associations in mouse models are correlative in human patients. In the instant case, thought there is a correlation of increased midkine expression in a mouse model, there is unpredictability that the same correlation of increased midkine expression in humans with regard to increased potential to lupus can be observed. Based on the teachings of the art (Kotzin 1, Kotzin 2, Liu et al., and Morel) it is unpredictable that such correlations can be directly extrapolated, rather, each association must be tested individually in a human sample without a guarantee of success.

(G) The reply asserts that the specification teaches the midkine expression levels in mouse models (p. 8 1st full paragraph). The specification asserts that the specification teaches that the midkine gene is found in humans (p. 8 1st full paragraph). The reply asserts that it would not be undue experimentation to measure the levels of midkine gene expression in humans and compare to a reference to determine if the human has an increased likelihood of lupus nephritis (p. 8 1st full paragraph).

This argument has been fully considered but has not been found persuasive.

Based on the teachings of the art (Kotzin 1, Kotzin 2, Liu et al., and Morel) it is unpredictable that such correlations can be directly extrapolated, rather, each association must be tested individually in a human sample without a guarantee of success. The midkine gene expression and correlation to susceptibility in lupus would have to be determined in a human population. This would require many intervening steps without predictable success. As shown by Liu et al. gene expression in mouse models do not overlap with human expression data. Therefore, it would be unpredictable that an increase in the midkine gene in the mouse model would be correlative to an increase in a human sample.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER